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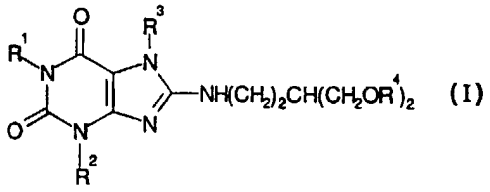

(I)

(57) Abstract

A compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a): $-(CH_2)_m$-A wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical; R^3 represents hydrogen, substituted or unsubstituted alkyl or an aralkyl group substituted or unsubstituted in the aryl moiety; and R^4 represents hydrogen, alkyl or alkylcarbonyl; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

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8-SUBSTITUTED HANTHINES AS PHOSPHODIESTERASE INHIBITORS

The present invention relates to certain novel compounds having pharmacological activity, to a process for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Molecular Pharmacology, Volume 6, No. 6, 1970, p.597-603 discloses 1,3-dimethyl-8-nitro-xanthine. This compound is disclosed as having lipolytic activity. Ann Chim, 47, 362-365 (1957) discloses 1,3-dimethyl-8-amino-xanthine and a process by which it may be prepared. No pharmacological utility is disclosed for this compound. Drug Res. 27(1) Nr 19, 1977, pages 4-14, Van K.H. Klingler discloses certain 1,3-dimethyl- 8-substituted xanthines as intermediates solely in the synthesis of phenylethyl aminoalkyl xanthines. Drug Res. 31 (11), Nr. 12, 1981, R.G. Werner *et al*, pages 2044-2048 discloses certain 1,3-dimethyl-8-substituted xanthines. No pharmacological activity is disclosed for these compounds.

European Patent Application, Publication Number 0369744 also discloses certain 1,3- or 1,3,7- 8-H cycloalkylalkylene xanthines, for use *inter alia* as bronchodilators in the treatment of asthma.

It has now been discovered that a novel series of 8-substituted xanthines show activity as phosphodiesterase inhibitors.

These compounds are indicated to be good inhibitors of induced blood eosinophilia and that they are therefore potentially useful in the treatment and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

These compounds are also indicated to have bronchodilator activity and thus to be of potential use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

These compounds also have a protective effect against the consequences of cerebral metabolic inhibition. The said compounds improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated with Parkinson's disease.

These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the compound is indicated to be of benefit for the treatment of functional disorders resulting from disturbed brain function following ischaemia.

These compounds are also active in increasing the oxygen tension in ischaemic skeletal muscle. This property results in an increase in the nutritional blood flow through ischaemic skeletal muscle which in turn indicates that the compounds of the invention are of potential use as agents for the treatment of peripheral vascular disease such as intermittent claudication.

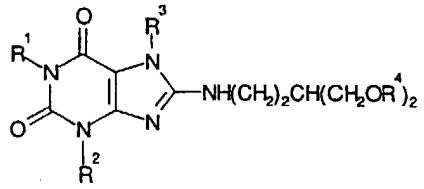
The present compounds are also considered to be inhibitors of the *in vivo* production of Tumor Necrosis Factor (TNF) and hence they have potential for the treatment of diseases associated with excessive or unregulated TNF production including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or

pyresis. The present compounds are also useful in the treatment of viral infections that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the present compounds. Such viruses include for example HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex.

The above mentioned treatments of course include veterinary treatments and in particular they include the treatment of TNF mediated viral infections including, for example, feline immunodeficiency virus (FIV) or other retroviral infections such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

These compounds are also of potential use in the treatment of proliferative skin disease in human or non-human mammals.

Accordingly, the invention also provides a compound of formula (I):



(I)

or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m-A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;

R^3 represents hydrogen, substituted or unsubstituted alkyl or an aralkyl group substituted or unsubstituted in the aryl moiety; and

R^4 represents hydrogen, alkyl or alkylcarbonyl.

Suitably, A is unsubstituted. Favourably, A represents a substituted or unsubstituted C_{3-8} cycloalkyl group, especially a C_{3-6} cycloalkyl group.

In particular, A represents a substituted or, preferably, unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

Favourably, A represents a cyclopropyl group or a cyclobutyl group.

Preferably, A represents a cyclopropyl group.

When R^3 represents unsubstituted alkyl, suitable examples include methyl.

When R^3 represents substituted alkyl, suitable examples include alkoxy methyl such as methoxymethyl.

Suitably, R^3 represents an aralkyl group, for example a benzyl group, substituted or unsubstitued in the aryl moiety.

When R^3 is a benzyl group, examples include unsubstituted benzyl or benzyl substituted in the phenyl moiety by methoxy groups, particular examples include 4-methoxy benzyl.

Suitably R^4 represents hydrogen.

Suitably, R^4 represents alkylcarbonyl.

Suitably alkycarbonyl groups are C_{1-4} alkylcarbonyl groups for example acetyl.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable base salts of the compounds of formula (I) include 7-N base salts including metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Suitable acid addition salts of the compounds of formula (I) are the acid addition salts including pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphonate, α-keto glutarate, α-glycerophosphate and glucose-1- phosphate. Preferably the acid addition salt is a hydrochloride salt.

The pharmaceutically acceptable salts of the compounds of formula (I) are prepared using conventional procedures.

When used herein the term 'cyclic hydrocarbon radical' includes single ring and fused ring, alicyclic hydrocarbons comprising up to 8 carbon atoms in each ring, suitably up to 6 carbon atoms, for example 3, 4, 5 or 6 carbon atoms.

Suitable optional substituents for any cyclic hydrocarbon radical includes a C_{1-6} alkyl group or a halogen atom.

When used herein the term 'aryl' whether used alone or as part of another group (for example in an aralkyl group) includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, halo alkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups. Optional substituents for any phenylene group include up to three of the substituents mentioned in relation to the aryl group.

Suitable optional substituents for the aryl moiety of any aralkyl group include those mentioned above in regard to the `aryl' group and in particular include alkoxy groups, for example methoxy groups.

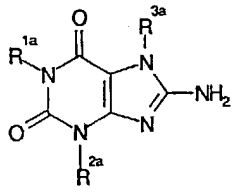
When used herein the term 'alkyl' whether used alone or when used as part of another group (for example as in an alkylcarbonyl group) includes straight and branched chain alkyl groups, containing from 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, for example methyl, ethyl, propyl or butyl. Suitable optional

substituents for any alkyl group include up to five, preferably up to three of the substituents mentioned above in relation to the aryl group.

When used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

The compounds of formula (I) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (I), which process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1 as defined in relation to formula (I) or a group convertible to R^1, R^{2a} represents R^2 as defined in relation to formula (I) or a group convertible thereto and R^{3a} represents R^3 as defined in relation to formula (I) or a group convertible to R^3,

with a compound of formula (III):

$$L^1\text{-}(CH_2)_2CH(CHOR^5)_2 \qquad (III)$$

wherein, R^5 represents a hydroxy protecting group and L^1 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) removing any protecting group;

(ii) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or R^{3a} to R^3;

(iii) converting a compound of formula (I) into a further compound of formula (I);

(iv) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

A suitable leaving group L^1 is a halo atom, especially an iodine atom.

The reaction between compounds of formulae (II) and (III) may be carried out using conventional alkylation conditions, for example in an aprotic solvent such as dimethoxyethane, dimethylformamide or tetrahydrofuran, at any temperature providing a suitable rate of formation of the required product, such as in the range of from 0°C to 100°C, conveniently in the range of from 40°C to 80°C, for example 60°C; and preferably in an inert atmosphere such as nitrogen.

Suitably the 8-amino group of compound (II) is in an activated form, favourably in an ionic form such as a salted form, for example an alkali metal salted form provided by treating the compound of formula (II) with an alkali metal base, for example potassium t-butoxide.

A compound of formula (II) may be prepared using methods described in European Patent Application, Publication No. 0389282.

The compounds of formula (III) are known compounds or they may be prepared according to methods used to prepare known compounds, for example those discussed in Tetrahedron (1990), **46**, 6903.

Conversions of one compound of formula (I) into another compound of formula (I) includes converting one group R^4 into another group R^4, for example hydrolysing compounds wherein R^4 represents an alkylcarbonyl group into a compound of formula (I) wherein R^4 represents a hydrogen atom.

In the said conversions the appropriate conventional procedures are suitably employed, hence in the abovementioned hydrolysis conventional hydrolysis conditions are used, for example the hydrolysis of an alkylcarbonyl group is effected by using mild basic hydrolysis preferably by means of potassium carbonate in an ethanolic solution such as methanol, conveniently at ambient temperature.

Suitable values for R^{1a} and R^{2a} include R^1 and R^2 respectively or nitrogen protecting groups such as benzyl, nitrobenzyl or trimethoxybenzyl groups. Suitable values for R^{3a} include R^3.

Suitably, when R is substituted or unsubstituted aralkyl, R^{1a} and R^{2a} represent nitrogen protecting groups which can be inserted and removed without affecting R^3, for example trimethylsilyl groups.

Preferably, when R^3 is substituted or unsubstituted aralkyl then R^{1a} is R^1 and R^{2a} is R^2.

When R^{1a}, R^{2a} or R^{3a} represents other than R^1, R^2 or R^3 repectively, the abovementioned conversions of R^{1a} into R^1, R^{2a} to R^2 and R^{3a} into R^3 may be carried out using the appropriate conventional procedure. For example when R^{1a} (or R^{2a}) represents a nitrogen protecting group, such as a benzyl group, the protecting group may be removed using the appropriate conventional procedure, such as catalytic hydrogenation, and the resulting product reacted with a compound of formula (IV):

$$X\text{-}(CH_2)_m\text{-}A \qquad (IV)$$

wherein A and m are as defined in relation to formula (IA) and X represents a leaving group, such as halide, for example bromide or iodide.

The protection of any reactive group or atom, such as the xanthine nitrogen atom may be carried out at any appropriate stage in the aforementioned process. Suitable protecting groups include those used conventionally in the art for the particular group or atom being protected, for example suitable protecting groups for the xanthine nitrogen atoms are alkylsilyl groups, especially trimethylsilyl or t-butyldimethylsilyl groups.

Protecting groups may be prepared and removed using the appropriate conventional procedure: For example, alkylsilyl protecting groups may be prepared by treating the compound of formula (II) with an appropriate alkylsilyl halide, for example trimethylsilyl chloride for trimethylsilyl groups and t-butyldimethylsilyl chloride for t-butyldimethylsilyl groups. The silyl protecting groups may be removed by treatment with t-butylammonium fluoride in a suitable solvent, such as tetrahydrofuran conveniently at an ambient temperature.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: the present invention accordingly provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

In a further aspect the present invention also provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a

Opharmaceutically acceptable solvate thereof, for use as a phosphodiesterase inhibitor.

In a particular aspect, as indicated hereinbefore, the present invention provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

In a further particular aspect, the present invention provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatments mentioned hereinbefore, such as cerebral vascular and neuronal denerative disorders associated with learning, memory and cognitive dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events.

In a further aspect there is provided a compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an inhibitor of the *in vivo* production of Tumor Necrosis Factor (TNF).

Particularly, there compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of diseases associated with excessive or unregulated TNF production.

Diseases associated with excessive or unregulated TNF production include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired

immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

In a further aspect there is provided a compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of viral infections that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the present compounds. Such viruses include for example HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex.

A compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (I), or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (I) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day; and such therapy may extend for a number of weeks or months.

When used herein the term 'pharmaceutically acceptable' encompasses materials suitable for both human and veterinary use. No toxicological effects have been established for the compounds of formula (I) in the abovementioned dosage ranges.

The following pharmacological data and examples illustrate the invention. The following preparations illustrate the preparation of intermediates to the novel compounds of formula (I).

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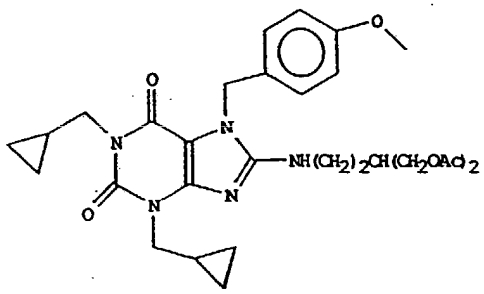
EXAMPLE 1

8-[4-Acetoxy-3-(acetoxymethyl)butylamino]-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine



Potassium t-butoxide (0.35 g, 3.13 mmol) was added to a solution of 8-amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (0.99 g, 2.5 mmol) in dimethoxyethane (DME 10 ml) at 60 °C under nitrogen. After 3h a solution of 4-acetoxy-3-(acetoxymethyl)butyl iodide (1.69 g, 5.4 mmol) in DME (3 ml) was slowly added over 5 min. After stirring for 18 h the mixture was cooled, poured into ethyl acetate and the organic solution washed with water, dried and evaporated. Chromatography (acetone/hexane 1:7) on silica gave 8-[4-acetoxy-(3-acetoxymethyl)butyl-amino]- 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-xanthine (0.63 g, 43%) mp 129-129.5 °C;

δ ($CDCl_3$) 0.43-0.50 (8H, m), 1.26-1.38 (2H,m), 1.58 (2H,m), 1.91 (1H,m), 2.05 (6H,s), 3.47 (2H,m), 3.79 (3H,s), 3.90 (2H,d,J=3.9Hz), 3.93 (2H,d,J=3.9Hz), 4.03 (4H,m), 4.30 (1H,t,J=6.0Hz), 5.29 (2H,s), 6.88 (2H,d,J=8.5Hz) and 7.22 (2H,d,J=8.5Hz);

ν_{max} (KBr) 3272 (m), 1742 (s), 1693 (s), 1651 (s), 1617 (s), 1566 (s), 1250 (s), 1240 (s), 1221 (s) and 1040 (s) cm^{-1};

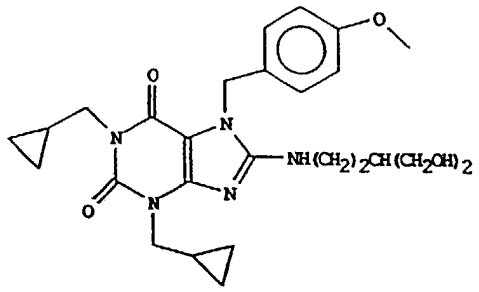
m/e (FAB) 121 (100%), 145 (34), 105 (27), 582 (MH^+,25) and 604 (MNa^+, 15);

Found C, 61.78; H, 6.89; N, 11.82; $C_{30}H_{39}N_5O_7$ requires C, 61.94; H, 6.76; N, 12.04%

followed by starting material (0.41g, 42%) identical to an authentic sample.

EXAMPLE 2

1,3-Di(cyclopropylmethyl)-8-[4-hydroxy-3-(hydroxymethyl)butylamino]-7-(4-methoxybenzyl)xanthine



8-(4-Acetoxy-3-(acetoxymethyl)butylamino)-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (0.22 g, 0.37 mmol) and potassium carbonate (0.005 g, 0.037 mmol) were stirred in methanol (8 ml) at room temperature for 5 h. The mixture was neutralised with cHCl and the solvent removed under reduced pressure. Chromatography of the residue (250 mg) on silica (hexane/acetone gradient) yielded 1,3-di(cyclopropylmethyl)-8-[4-hydroxy-3-(hydroxymethyl)butylamino)-7-(4-methoxy benzyl)xanthine (0.11 g, 59%), mp. 141-2°C;

δ ($CDCl_3$) 0.39-0.49 (8H,m), 1.28-1.38 (2H,m), 1.61-1.65 (3H,m), 2.29 (2H,t,J=4.5Hz), 3.46 (2H,m), 3.68 (4H,br s), 3.80 (3H,s), 3.92 (4H,t (overlapping d),J=6.5Hz), 4.56 (1H,t,J=5.3Hz); 5.28 (2H,s), 6.88 (2H,d,J=8.5Hz) and 7.23 (2H,d,J=8.5Hz);

ν_{max} (KBr) 3314 (m), 3250 (s), 1695 (s), 1685 (s), 1634

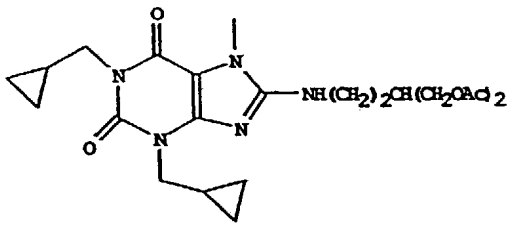
(s), 1611 (s), 1607 (s), 1578 (m), 1030 (m) and 756 (m) cm^{-1};

m/e (CI) 498 (MH^+, 100%), 35 (40), 448 (12), 396 (10) and 121 (7);

Found C, 62.92; H, 7.10; N, 14.22; $C_{26}H_{35}N_5O_5$ requires C, 62.76; H, 7.09; N, 14.08%.

EXAMPLE 3

8-[4-Acetoxy-3-(acetoxymethyl)butylamino]-1,3-di(cyclopropylmethyl)-7-methylxanthine



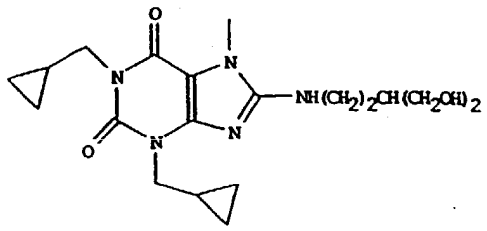
8-[4-Acetoxy-3-(acetoxymethyl)butylamino]-1,3-di(cyclopropylmethyl)-7-methylxanthine was prepared from 8-Amino-1,3-di(cyclopropylmethyl)-7-methylxanthine in 32% yield in an identical manner to Example 1 , mp 163-4°C;

δ ($CDCl_3$) 0.41-0.49 (8H,m), 1.24-1.37 (2H,m), 1.72 (2H,q,J=6.9Hz), 2.08 (6H,s), 2.13 (1H,t,J=6.3Hz), 3.59 (2H,dt,J=6.9,6.0Hz), 3.68 (3H,s), 3.90 (4H,t (overlapping d), J=7.0 Hz), 4.06-4.20 (4H,m), 4.50 (1H,t,J=6.0Hz);

Found C, 58.05; H, 6.97; N, 14.53; $C_{23}H_{33}N_5O_6$ requires C, 58.09; H, 6.99; N, 14.73%.

EXAMPLE 4

1,3-Di(cyclopropylmethyl)-8-[4-hydroxy-3-(hydroxymethyl)butylamino]-7-methylxanthine



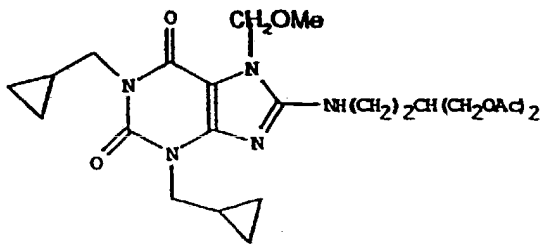
1,3-Di(cyclopropylmethyl)-8-[4-hydroxy-3-(hydroxymethyl)butylamino]-7-methylxanthine was prepared from 8-[4-acetoxy-3-(acetoxymethyl)butylamino]-1,3-di(cyclopropylmethyl)-7-methyl xanthine in 59% yield in an identical manner to Example 2, mp 173°C;

δ ($CDCl_3$) 0.39-0.48 (8H,m), 1.25-1.39 (2H,m), 1.69 (2H,q,J=6.6Hz), 1.83 (1H,m), 3.49 (2H,m), 3.64 (3H,s), 3.67 (4H,t,J=5.5Hz), 3.87 (2H,d,J=7.2Hz), 3.91 (2H,d,J=7.2Hz), 4.04 (2H,t,J=5.5Hz), 6.17 (1H,t,J=5.5Hz).

Found C, 58.11; H, 7.56; N, 17.98; $C_{19}H_{29}N_5O_4$ requires C, 58.29; H, 7.47; N, 17.89%.

Example 5

8-[4-Acetoxy-3-(acetoxymethyl)butylamino]-1,3-di(cyclopropylmethyl)-7-(methoxymethyl)xanthine



The title compound (mp 98-99°C) was prepared using an analogous procedure to that described in Example 1.

PHARMACOLOGICAL DATA

Inhibition of Phosphodiesterase

Isolation of phosphodiesterases

The Ca^{2+}/calmodulin-stimulated PDE (PDE I, see Table 1 and Beavo and Reifsynder (1990) for nomenclature) was prepared from bovine cardiac ventricle. Following chromatography on a Mono Q column, the fractions showing stimulation of PDE activity by Ca^{2+} and calmodulin were pooled and further purified on a calmodulin-affinity column. cGMP-stimulated PDE (PDE II), cGMP-inhibited PDE (PDE III) and cAMP-specific PDE (PDE IV) were all isolated from guinea-pig cardiac ventricle. Initial chromatography on a 20 ml Mono Q column resolved PDE III from a peak that contained both PDE II and PDE IV. The latter were separately rechromatographed on a 1 ml Mono Q column. cGMP-selective PDE (PDE V) was obtained from porcine lung using chromatography on DEAE-cellulose and Mono Q columns; a calmodulin-affinity column was used to remove residual PDE I activity.

Characteristics of phosphodiesterase isoenzymes

With the exception of PDE II, which displayed positive cooperativity, all the preparations showed simple Michaelis-Menton kinetics (see Table 1).

PDE I The activity of this isoenzyme was stimulated by the Ca^{2+}- calmodulin complex. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate.

PDE II The activity of this isoenzyme with cAMP as a substrate was stimulated by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate under basal conditions. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

PDEIII The activity of this isoenzyme with cAMP as a substrate was inhibited by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the former was

the preferred substrate. The activity of this isoenzyme was unaffected by the Ca^{2+} calmodulin complex.

PDE IV This isoenzyme had high affinity for cAMP, the hydrolysis of which was not inhibited by cGMP. The activity of this isoenzyme was unaffected by the Ca2-calmodulin complex.

PDE VThis isoenzyme had high affinity for cGMP. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

Assay of phosphodiesterase activity

PDE activity was assayed by the boronate column method as previously described (Reeves et. al., 1987). The enzymes were assayed by incubation at 37°C for 4-30 min. in 50 mM Tris, 5 mM $MgCl_2$, pH 7.5 with ^3H-labelled cyclic nucleotide (4 x 10^5 disintegrations min^{-1}) and ^{14}C-labelled nucleotide 5'-monophosphate (3 x 10^3 disintegrations min^{-1}). The assay was stopped by boiling and the ^3H-labelled 5'-monophosphate product separated from substrate on boronate columns. The reaction mixture was diluted with 0.5 mL 100 mM HEPES [N-(2-hydroxyethyl)piperazine-N^1-2-ethanesulfonic acid], 100 mM NaCl, pH 8.5, and applied to the column. The column was extensively washed with the same buffer, and the 5'-nucleotide eluted with 6 mL of 0.25 M acetic acid. The recovery of product as judged by ^{14}C-recovery was approximately 80%. All assays were linear with time of incubation and concentration of enzyme over the range used in these experiments.

IC_{50} values (the concentration of inhibitor required for 50% inhibition of activity) were obtained by incubation of the isoenzyme using 1 µM cGMP as a substrate for PDE I (in the absence of Ca^{2+} and calmodulin), PDE II and PDE V and with 1 µM cAMP as a substrate for PDE III and PDE IV.

A range of inhibitor concentrations from 0.1 x IC_{50} to 100 x IC_{50} was used.

References

BEAVO, J.A. and D.H. REIFSNYDER, Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. Trends. Pharmacol. Sci. 11, 150-155 (1990).

REEVES M.L., B.K. LEIGH and P.J. ENGLAND, The identification of a new cyclic nucleotide phosphodiesterase activity in human and guinea-pig cardiac ventricle. Biochem. J. 241, 535-541 (1987).

Table 1: Kinetic properties of phosphodiesterase isoenzymes

Isoenzyme		Km (μM)		Vmax cAMP
		cAMP	cGMP	Vmax cGMP
I.	Ca^{2+}/calmodulin-stimulated	36	5	5
II.	cGMP-stimulated	45	14	1
III.	cGMP-inhibited	0.5	0.1	5
IV.	cAMP-specific	2	>	n.d.
V.	cGMP-specific	>	1	N.d.

a enzyme displayed positive cooperativity

\> Km > 100 μM

n.d. not determined, due to inability of PDE to hydrolyse one of the substrates.

RESULTS

EXAMPLE NO.	INHIBITION OF:
	PDE VA	PDE IV
	(IC_{50}μM)	
1	0.2	3
2	0.2	9

Inhibitory Effect of compounds of Formula (I) on in vitro TNF production by Human Monocytes

Section I: Assay set-up

The effects of compounds of Formula (I) on the in vitro production of TNF by human monocytes was examined using the following protocol.

Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. et al., J. Immunol., 132(2):936 (1984). The monocytes were plated at a density of 1 X 10^6 cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and 1 ml fresh medium (RPMI-1640 (Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum and penicillin and streptomycin at 10 units/ml was added. The cells were incubated for 45 minutes in the presence or absence of test compounds at 1nM-10uM dose ranges (compounds were solubilized in Dimethyl-sulfoxide/Ethanol such that the final solvent concentration in the culture medium was 0.5% Dimethyl sulfoxide/0.5% Ethanol). Bacterial lipopolysaccharide (E. coli 055:B5 [LPS] from Sigma Chemicals Co.) was then added at 100 ng/ml in 10 ml Phosphate Buffered Saline (PBS) and cultures incubated for 16-18 hours at 37°C in a 5% CO_2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 revolutions per minute (rpm) to remove cell debris and .05 ml of the supernatant assayed for TNF activity using the radioimmunoassay described below.

Section II: Radioimmunoassay procedure for TNF activity

The assay buffer consisted of 0.01M $NaPO_4$, 0.15M NaCl, 0.025M EDTA and 0.1% sodium azide at pH 7.4. Human recombinant TNF (rhTNF) obtained using the procedure of Chen et al., Nature, 330:581-583 (1987) was iodinated by a modified Chloramine-T method described in Section III below. To samples (50 µl culture supernatants) or rhTNF standards, a 1/9000 dilution of polyclonal rabbit anti-rhTNF (Genzyme, Boston, MA) and 8000 cpm of ^{125}I-TNF was added in a final volume of 400 µl buffer and incubated overnight (18 hours) at 4°C. Normal rabbit serum and goat anti-rabbit IgG (Calbiochem) were titrated against each other for maximum precipitation of the anti-rhTNF. The appropriate dilutions of carrier normal rabbit serum (1/200), goat anti-rabbit IgG (1/4) and 25 Units

heparin (Calbiochem) were allowed to precipitate and 200 µl of this complex was added per assay tube and incubated overnight at 4°C. Tubes were centrifuged for 30 minutes at 2000 rpm, supernatants were carefully aspirated, and radioactivity associated with the pellets measured in a Beckman Gamma 5500 counter. The logit-log linear transformation curve was used for the calculations. The concentrations of TNF in the samples was read from a standard curve of rhTNF that was linear in the 157 to 20,000 pg/ml range.

Section III: Radioiodination of rhTNF

Iodination of rhTNF was performed using a modified chloramine-T method of Frolik et al., J. Biol. Chem., 259:10995-11000 (1984). Briefly, 5 mg of rhTNF in 5 ml of 20MM Tris ph 7.5, was diluted with 15 ml of 0.5M KPO_4 and 10 ml of carrier free ^{125}I(100mCi/ml;ICN). To initiate the reaction, a 5ml aliquot of a 100mg/ml (aqueous) chloramine-T solution was added. After 2 minutes at room temperature, an additional 5 ml aliquot was added followed 1.5 minutes later by a final 5 ml addition of chloramine-T. The reaction was stopped 1 minute later by sequential addition of 20 ml of 50mM Sodium Metabisulfite, 100 ml of 120mM Potassium Iodide and 200 ml of 1.2 mg/ml Urea. The contents were mixed and the reaction mixture was passed over a pre-packed Sephadex G-25 column (PD 10 Pharmacia), equilibrated and eluted with Phosphate Buffered Saline pH 7.4 containing 0.25% gelatin. The peak radioactivity containing fractions were pooled and stored at -20°C. Specific activity of ^{125}I-TNF was 80-100 mCi/mg protein. Biological activity of iodinated TNF was measured by the L929 cytotoxicity assay of Neale, M.L. et al., Eur. J. Can. Clin. Oncol., 25(1):133-137 (1989) and was found to be 80% that of unlabeled TNF.

Section IV: Measurement of TNF- ELISA:

Levels of TNF were also measured using a modification of the basic sandwich ELISA assay method described in Winston et al., Current Protocols in Molecular Biology, Page 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York, USA The ELISA employed a murine monoclonal anti-human TNF antibody, described below, as the capture antibody and a polyclonal rabbit anti-human TNF , described below, as the second antibody. For detection, a peroxidase-conjugated goat anti-rabbit antibody (Boehringer Mannheim, Indianopolis, Indiana, USA, Catalog # 605222) was added followed by a substrate for peroxidase (1mg/ml orthophenylenediamine with 0.1% urea peroxide). TNF

levels in samples were calculated from a standard curve generated with recombinant human TNF produced in E. Coli (obtained from SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA).

Section V: Production of anti-human TNF antibodies:

Monoclonal antibodies to human TNF were prepared from spleens of BALB/c mice immunized with recombinant human TNF using a modification of the method of Kohler and Millstein, Nature 256:495 (1975), the entire disclosure of which is hereby incorporated by reference. Polyclonal rabbit anti-human TNF antibodies were prepared by repeated immunization of New Zeland White (NZW) rabbits with recombinant human TNF emulsified in complete Freund's adjuvant (DIFCO, IL., USA).

Results:

It has been determined that 8-(4-Acetoxy-3-acetoxymethyl)-1-butylamino-1,3-di(cyclopropylmethyl)-7-p-methoxybenzyl xanthine demonstrated an IC_{50} of about 0.30 μM in the in-vitro TNF production assay system.

Endotoxin Shock in D-gal-Sensitized Mice

The protocol is essentially as described in Galanos et al., Proc. Nat'l Acad. Sci USA, 76:5939-43 (1979) whose disclosure is herein incorporated by reference. Briefly, D-gal (D(+) Galactosidase) sensitizes various strains of mice to the lethal effects of endotoxin. The administration of D-gal (300-500mg/kg) intra-venously (i.v.) sensitizes the mice to doses of lipopolysaccharide (LPS) as low as 0.1μg. Briefly, male C57BL/6 mice, obtained from Charles River Laboratories (Stone Ridge, New York, USA) of 6-12 weeks of age are injected i.v. with 0.1 μg of LPS from Salmonella typhosa (Difco Laboratories, Detroit, Michigan, USA) admixed with D(+)-gal (Sigma; 500 mg/kg) in 0.20-0.25 ml pyrogen-free saline. Compounds to be tested are administered at various times prior to or following the i.v. injection of LPS/D-gal. In this model, the control animals usually die 5-6 hr. following the injection of LPS, although on occasion deaths are seen between 24 and 48 hr.

Measurement of TNF Activity

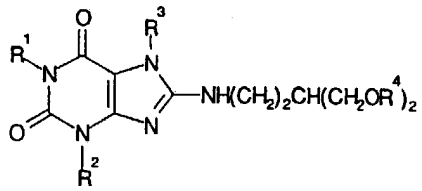
Plasma levels of TNF are measured using a modification of the basic sandwich ELISA method described in Winston et al., Current Protocols in Molecular Biology, Pg. 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York , USA. The Elisa employed a hampster monoclonal anti-mouse TNF

(Genzyme, Boston, MA, USA) as the capture antibody and a polyclonal rabbit anti-murine TNF (Genzyme, Boston, MA, USA) as the detecting antibody. TNF levels in mouse samples are calculated from a standard curve generated with recombinant murine TNF (Genzyme, Boston, MA , USA). TNF levels determined by ELISA correlated with levels detected by the L929 bioassay of Ruff et. al., J. Immunol. 125:1671-1677 (1980), with 1 Unit of activity in the bioassay corresponding to 70 picograms (pg) of TNF in the ELISA. The ELISA detected levels of TNF down to 25 pg/ml.

Active compounds provide a positive in-vivo response in the above noted model and for example demonstrate an ED_{50} for reduction of serum TNF of about $\geq$ 50 mg/kg orally.

Claims

1. A compound of formula (I):



(I)

or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m-A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;
R^3 represents hydrogen, substituted or unsubstituted alkyl or an aralkyl group substituted or unsubstituted in the aryl moiety; and
R^4 represents hydrogen, alkyl or alkylcarbonyl.

2. A compound according to claim 1, wherein A represents a cyclopropyl group.

3. A compound according to claim 1 or claim 2, wherein R^3 represents an aralkyl group.

4. A compound according to any one of claims 1 to 3, wherein R^3 represents a substituted or unsubstituted benzyl group.

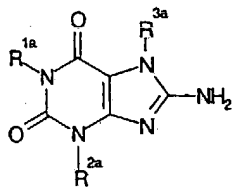
5. A compound according to any one of claims 1 to 4, wherein R^3 represents a 4-methoxy benzyl group.

6. A compound according to any one of claims 1 to 5, wherein R^4 represents hydrogen.

7. A compound according to any one of claim 1 to 5, wherein R^4 represents alkylcarbonyl.

8. A compound according to claim 1 selected from any one of Examples 1 to 28 herein.

9. A process for preparing a compound of formula (I), which process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1 as defined in relation to formula (I) or a group convertible to R^1, R^{2a} represents R^2 as defined in relation to formula (I) or a group convertible thereto and R^{3a} represents R^3 as defined in relation to formula (I) or a group convertible to R^3,

with a compound of formula (III):

$$L^1\text{-}(CH_2)_2CH(CHOR^5)_2 \quad \text{(III)}$$

wherein, R^5 represents a hydroxy protecting group and L^1 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) removing any protecting group;

(ii) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or R^{3a} to R^3;

(iii) converting a compound of formula (I) into a further compound of formula (I);

(iv) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound of formula (I), wherein L^1 is a halo atom, especially an iodine atom.

11. A pharmaceutical composition comprising a compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

12. A compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

13. A compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an inhibitor of the *in vivo* production of Tumor Necrosis Factor (TNF).

14. A compound of formula (I) or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of diseases associated with excessive or unregulated TNF production.

15. A use according to claim 14, wherein the treatment is the treatment and/or prophylaxis of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

16. A use according to claim 14, wherein the treatment is the treatment and/or prophylaxis of viral infections that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the present compounds. Such viruses include for example HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the

Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/01014

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D473/06; A61K31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 258 191 (SANDOZ-PATENT) 2 March 1988 *Document*	1-16
A	EP,A,0 389 282 (BEECHAM-WUELFING) 26 September 1990 see page 20 - page 22; claims	1-16
A	EP,A,0 386 683 (POLI INDUSTRIA CHIMICA) 12 September 1990 *Document*	1-16
A	WO,A,9 205 176 (BEECHAM) 2 April 1992 see page 33 - page 37; claims	1-16
A	WO,A,9 205 175 (BEECHAM) 2 April 1992 see page 47 - page 51; claims	1-16

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 SEPTEMBER 1993	14. 09. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	WO,A,9 211 260 (BEECHAM) 9 July 1992 see page 54 - page 58; claims	1-16

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9301014
SA 74603

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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